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3 Fatty Acids", THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 318, No. 9, pages 549-557 (March 3, 1988), (referred to as "Alexander, *et al.*" by the Examiner, and hereinafter referred to synonymously as "Leaf" and "the Leaf Article").

Prior to addressing the substantive merits of the Examiner's rejection based upon the combination of Miettinen and Leaf, Applicant respectfully notes that the Leaf Article has not been made of record. Applicant has not cited the Leaf Article, nor has the Examiner listed the reference on a Form PTO-892. As the Examiner has relied upon the teachings of the Leaf Article in formulating the rejection mentioned above, as set forth in Paper No. 7, the reference should have been listed on a Form PTO-892. In an effort to ensure that this reference appears on the face on any patent which issues based upon the instant application, Applicant has enclosed a copy of a Form PTO-1449 listing the Leaf Article for the Examiner's convenience. Applicant respectfully requests that the Examiner enclose an initialed copy of the enclosed Form PTO-1449 along with her next communication to Applicant's undersigned representative, clearly indicating consideration of the listed reference.

In Paper No. 7, the Examiner contends that Miettinen teaches a "fatty acid composition of β -sitostanol ester mixtures containing large amount [sic] of monoenes and polyenes", and that Miettinen teaches an enhanced efficacy of such compositions in lowering serum cholesterol levels, citing lines 40-45 and 56-68 of page 4, and Examples 1-3. (See, Paper No. 7, pp. 2-3). The Examiner acknowledges that Miettinen fails to teach phytostenol esters of conjugated acids, or the use thereof in reducing serum cholesterol levels. (See, Paper No. 7, p. 3). The Examiner also contends that the Leaf Article teaches "n-3 fatty acids for lowering the low-density lipoprotein (LDL) cholesterol", citing the last paragraph of column 2, at page 549. (*Id.*).

The Examiner further contends that Miettinen and Leaf are "from the same field", and thus, argues that they are combinable. (*Id.*). The Examiner further argues that the teachings of Miettinen and Leaf provide one of ordinary skill in the art with "ample" motivation to

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combine their teachings, and to modify their teachings to arrive at a phytosterol ester of a conjugated fatty acid, for use in reducing serum cholesterol levels. (*Id.*) The Examiner argues that sterol esters and omega-3 fatty acids are individually known for lowering cholesterol and triglyceride levels, based upon the cited art, and that their combination to achieve the same result would have been obvious.

Applicant strenuously, but respectfully, traverses the Examiner's rejection and the arguments and contentions in support thereof, as explained in more detail below. Initially, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness based upon the cited references.

It is well-settled that in order to establish a *prima facie* case of obviousness, and thus shift the burden of proving non-obviousness onto Applicant, the Examiner must show all of the following three criteria: (1) there must be some suggestion or motivation to modify or combine the references as suggested by the Examiner (it is not sufficient to say that the cited references can be combined or modified without a teaching in the prior art to suggest the desirability of the modification); (2) there must also be a reasonable expectation of success; and (3) the references as combined must collectively teach or suggest all limitations of the claims. The teaching or suggestion to combine and modify the cited art and the reasonable expectation of success must both be found in the prior art and not in the Applicant's Specification. (M.P.E.P. §2143).

None of the three criteria necessary to establish such a *prima facie* case of obviousness has been satisfied.

To begin with, one aspect of Applicant's claimed invention is directed to methods of reducing serum cholesterol content in a mammal, comprising: (i) providing a hypocholesteremic preparation comprising at least one phytosterol ester of a conjugated fatty acid having from about 6 to about 24 carbon atoms; and (ii) administering the hypocholesteremic preparation to a mammal in an amount effective to reduce serum cholesterol content in the mammal. Another aspect of Applicant's claimed invention is directed to hypocholesteremic

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preparations comprising at least one phytosterol ester of a conjugated fatty acid having from about 6 to about 24 carbon atoms. Hypocholesteremic preparations, and methods for their use, in accordance with Applicant's claimed invention surprisingly exhibit significantly improved cholesterol reducing activity over phytosterol derivatives derived from non-conjugated fatty acids. (See, e.g., Applicant's Specification, page 2, lines 22-29). It is a significant advantage to use a phytosterol ester having such increased activities when preparing foodstuffs, where increased concentration of additives, such a phytosterol esters, can negatively affect the taste and/or other aesthetic properties of the foodstuff. (See, e.g., Applicant's Specification, page 2, lines 1-5).

Contrary to the Examiner's broad assertion that Miettinen teaches β -sitostanol fatty acid ester mixtures containing large amounts of monoenes and polyenes, Miettinen only notes that "the β -sitostanol fatty acid ester mixture can be selected so as to contain large amounts of monoenes and polyenes," (Page 4, lines 40-41). Miettinen makes no mention of conjugation, nor any reference to fatty fish acids for that matter. Moreover, Miettinen provides no further guidance as to how the mixture "can be selected" so as to contain monoenes and polyenes. Miettinen discloses the use of vegetable oils in general, and specifically mentions rapeseed oil, coconut oil, sunflower oil, soybean oil, olive oil and corn oil. It is respectfully submitted that most common vegetable oils, in general, do not contain any significant amounts of conjugated fatty acids. Miettinen simply does not teach esters of phytosterols and conjugated fatty acids, nor does the reference suggest such esters. Reference to unsaturation does not, by itself, require any conjugation. Moreover, reference to polyunsaturation does not necessarily mean that any conjugation exists.

Furthermore, Applicant respectfully submits that the Examiner's arguments pertaining to the Leaf Article are incorrect, and inaccurate. The Examiner argues that the Leaf Article "alleviates the deficiency of Miettinen et al. because it teaches the n-3 fatty acids for lowering the low-density lipoprotein (LDL) cholesterol." (See, Paper No. 7, p. 3). While the Examiner is correct that the Leaf Article teaches lowered levels of LDL cholesterol in the blood

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of Eskimos whose diets included large amounts of long chain n-3 polyunsaturated fatty acids, which are commonly found in the fish which make up a large portion of the Eskimos' diet, this teaching is not adequate to alleviate any of the deficiencies of the Miettinen reference. The Leaf Article is directed to the effects of n-3 and n-6 polyunsaturated fatty acids. The designations, "n-3" and "n-6", refer to the number of carbon atoms from the methyl-terminus of the fatty acid at which the first unsaturation is located. None of the fatty acids identified in the Leaf Article is conjugated. All of the acids illustrated in Figures 1 & 2, at page 550, as cited by the Examiner, are specifically not conjugated. For example, the linoleic acid shown is 9,12 linoleic acid. The α -linolenic acid is 9,12,15-linolenic acid. Conjugation of said acids would require double bond locations at 9,11 and 9,11,13 respectively. In fact, none of the fatty acids identified in Figure 1 or 2 contains any multiple carbon-carbon double bonds separated by only one carbon-carbon single bond, *i.e.*, the definition of conjugation. The Leaf Article focuses on the differentiation in the body between n-3 and n-6 polyunsaturated fatty acids. There is no express teaching in the Leaf Article to ingest conjugated fatty acids, nor any teaching that such ingestion could be undertaken to reduce serum cholesterol levels.

The Examiner appears to address the lack of any express teaching with respect to conjugated fatty acids by noting that the Leaf Article also mentions "dietary fish and fish oil supplements". (*Id.*). Again, while the Leaf Article clearly references fish which contain the taught n-3 fatty acids, the reference makes no mention of any conjugation.

Moreover, as the Leaf Article specifically teaches the benefit of n-3 polyunsaturated fatty acids, all of which are not conjugated, it would appear that Leaf actually teaches away from hypocholesteremic preparations containing conjugated fatty acids, and instead focuses on the value of the more common, or more regular, "9,12" and "9,12,15" polyunsaturated fatty acids.

Thus, Applicant submits that neither reference, nor a combination thereof, teaches or suggests each and every element of the claimed invention. Specifically, neither reference teaches the use of conjugated fatty acids in lowering serum cholesterol levels. Moreover, neither

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reference teaches the use of an ester of a phytostenol compound with a conjugated fatty acid for such a purpose.

Secondly, Applicant submits that neither Miettinen, nor the Leaf Article, either alone or in combination, contains a teaching or suggestion which would motivate one of ordinary skill in the art to combine and modify their teachings, as suggested by the Examiner, in order to arrive at the claimed invention. As discussed above, neither reference teaches the use of conjugated fatty acids. In fact, the Leaf Article seems to emphasize the use of non-conjugated acids. Absent any specific teaching to use esters of conjugated fatty acids, it cannot reasonably be said that one of ordinary skill in the art would be motivated to modify the references to include the use of such esters. Moreover, based upon Leaf's apparent emphasis on non-conjugated acids, it could be said that the reference teaches away from the suggested modification.

Finally, given the lack of any teaching or suggestion of conjugated fatty acid esters of phytostenol compounds, and given the lack of any teaching or suggestion motivating such a modification of the prior art, one of ordinary skill in the art would not have a reasonable expectation of success, based upon the cited art.

Accordingly, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness, as none of the three criteria necessary to establish a *prima facie* case of obviousness has been satisfied. Thus, Applicant respectfully requests withdrawal of the rejection based upon Miettinen and the Leaf Article.

In a matter unrelated to the substantive shortcomings of the Examiner's rejection, Applicant would like to draw the Examiner's attention to, and specifically point out an error concerning an alleged election of species. In Paper No. 7, at page 3, line 9, the Examiner states, "[s]ee Fig. 2 for the elected species eicosapentaenoic acid." Applicant respectfully notes that no Species Election Requirement has been issued in the instant case. Accordingly, no election of any particular species has been made. Moreover, eicosapentaenoic acid is not conjugated, and thus, is not a species within the genus "conjugated fatty acids". Any limitation of search, scope

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or meaning which may be attributable to an election of species is improper in the instant application.

In Paper No. 7, the Examiner rejects claims 11-30 under 35 U.S.C. §103(a), as being unpatentable over European Patent Application No. EP1004594 of Burdick, *et al.* ("Burdick"). Applicant initially notes that the Examiner has also failed to list Burdick on a Form PTO-982. Additionally, Applicant notes that the Examiner has made several contentions and arguments with respect to the teachings of Burdick, specifically with respect to how such contended teachings somehow suggest Applicant's claimed invention.

While not agreeing with any of the Examiner's contentions or arguments in this regard, Applicant respectfully traverses this rejection on the basis that Burdick is not prior art. Burdick, European Patent Publication No. EP1004594A, published on May 31, 2000. The instant application has an International Filing Date of November 5, 1998. Burdick does not qualify as prior art under 35 U.S.C. §102, and thus, cannot form a proper basis for a rejection under 35 U.S.C. §103(a). Applicant respectfully requests withdrawal of the rejection based upon Burdick.

Even if it were assumed, for argument's sake, that a *prima facie* case of obviousness could be established based upon the cited references and that such a *prima facie* case of obviousness had been established, which it cannot and has not, any such alleged *prima facie* case of obviousness would be overcome by Applicant's showing of unexpected, significant improvements. As evidenced by the Examples set forth in Applicant's Specification, beginning at page 8, line 31, the phytostenol esters of conjugated fatty acids in accordance with certain preferred embodiments of Applicant's invention exhibit significant cholesterol reducing properties. The amount of cholesterol level reduction is significantly greater than phytostenol esters of non-conjugated fatty acids. As can be seen from Table 1, esters of conjugated fatty acids performed significantly better than polyunsaturated acid esters with no conjugation (such as those of linoleic acid). These significant improvements are surprising as noted in the Specification, at page 2, lines 22-29.

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It is submitted that Applicant's showing of unexpected and improved results sufficiently rebuts any alleged *prima facie* case of obviousness. Therefore, withdrawal of all rejections under 35 U.S.C. §103(a) is respectfully requested.

In view of the remarks set forth above, Applicant submit that all pending claims patentably distinguish over the prior art of record and known to Applicant, either alone or in combination. Accordingly, reconsideration, withdrawal of the rejection and a Notice of Allowance are respectfully requested.

Respectfully submitted,

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March 19, 2001
(Date)

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